



# 2-Dose HPV Vaccination Schedules: Review of Evidence

Lauri Markowitz, MD

Division of Viral Diseases

Advisory Committee on Immunization Practices

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# Overview

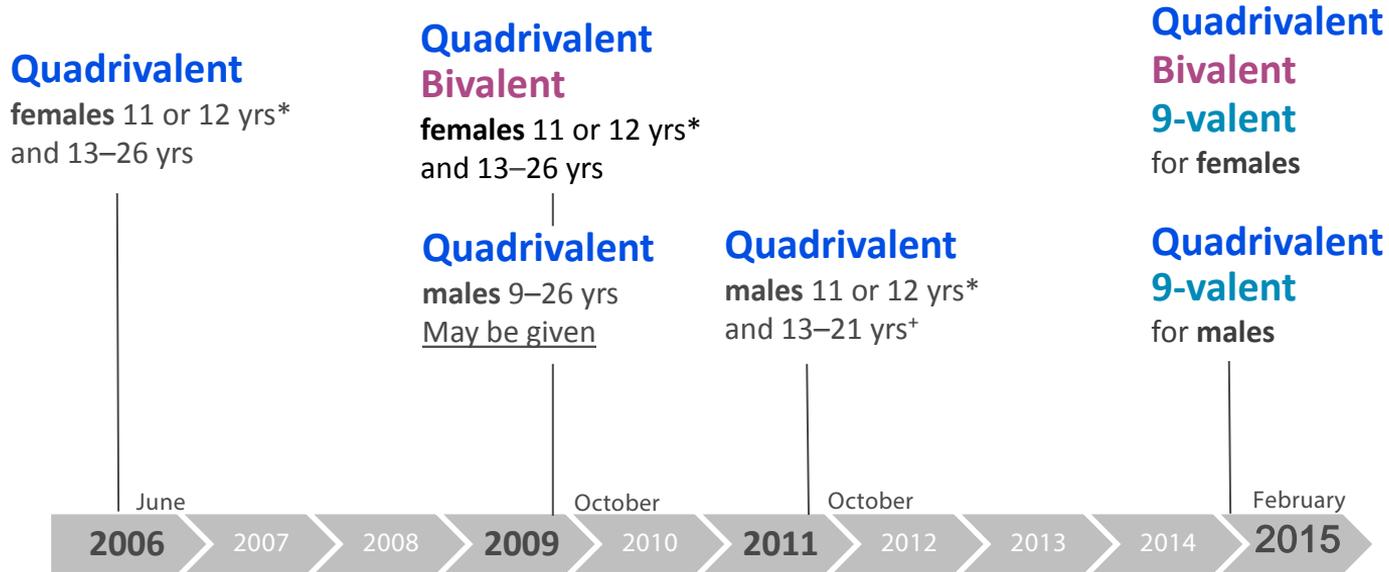
- Background on HPV vaccines and recommendations
- Summary of evidence on 2-dose schedules
- Vaccination coverage and programmatic considerations

# HPV Vaccines Licensed in the United States

	<b>Bivalent</b> 2vHPV (Cervarix)	<b>Quadrivalent</b> 4vHPV (Gardasil)	<b>9-Valent</b> 9vHPV (Gardasil 9)
<b>L1 VLP types</b>	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
<b>Manufacturer</b>	GlaxoSmithKline	Merck & Co.	Merck & Co.
<b>Adjuvant</b>	<b>AS04</b> 500 µg aluminum hydroxide 50 µg 3- <i>O</i> -desacyl-4'-monophosphoryl lipid A	<b>AAHS</b> 225 µg amorphous aluminum hydroxyphosphate sulfate	<b>AAHS</b> 500 µg amorphous aluminum hydroxyphosphate sulfate
<b>Licensed</b>	<b>2009</b>	<b>2006</b>	<b>2014</b>

L1, major capsid protein; VLP, virus-like particle

# Evolution of Recommendations for HPV Vaccination in the United States



**Recommended as 3-dose series**

\*Can be given starting at 9 years; +Vaccination is also recommended for men who have sex with men through age 26 years and for immunocompromised persons (including those with HIV infection), if not vaccinated previously; May be given to males age 22-26 years

# Current Recommendations for HPV Vaccination in the United States

- ACIP recommends routine vaccination at age 11 or 12 years. The series can be started beginning at age 9 years.
- Vaccination is recommended through age 26 years for females and through age 21 years for males not vaccinated previously.<sup>+</sup>
- 3-dose series (0, 1–2, 6 months)
- Vaccines
  - 2vHPV, 4vHPV or 9vHPV for females
  - 4vHPV or 9vHPV for males

<sup>+</sup>Vaccination is also recommended for men who have sex with men through age 26 years and for immunocompromised persons (including those with HIV infection), if not vaccinated previously; May be given to males age 22-26 years

# HPV Vaccine Use and Availability, United States

## HPV vaccine use

- Through 2014, almost all HPV vaccine used was 4vHPV
- In 2016, almost all HPV vaccine used is 9vHPV

## HPV vaccine availability

- GSK made a strategic business decision to stop supplying 2vHPV in U.S. due to low demand; 2vHPV supplies in U.S. expected to be used up by November 2016
- Only 9vHPV has been on CDC contracts since April 2016
- Merck will distribute only 9vHPV in U.S. after the end of October 2016
- 2vHPV and 4vHPV will continue to be available outside the U.S.

# Evidence on 2-dose HPV vaccine schedules

# Efficacy and Immunogenicity Data for Initial Licensure of HPV Vaccines – 3 Dose Schedule

- **Randomized controlled trials in 15–26 year olds**
  - Trial endpoints: cervical precancer lesions\*
- **Bridging immunogenicity trials in 9–15 year olds**
  - Licensure in this age group based on non-inferior antibody response compared with young adult women in efficacy trials

\*Future II Study Group, NEJM 2007; Garland, NEJM 2007; Paavonen, Lancet 2007

Quadrivalent vaccine trials had other outcomes as well including anal precancers in males, vulvar, vaginal precancers in females, genital warts in females and male

# Immunologic Basis of HPV Vaccination Schedules

- 3-dose schedule (0, 1-2, 6 months)
  - Considered “prime-prime-boost”
- 2-dose schedule (0, 6 months)
  - Considered “prime-boost”
- Memory B cells require at least 4-6 months to mature and differentiate into high-affinity B cells
  - ~6 month interval between first and last dose allows last dose to efficiently reactivate memory B cells

# Evidence Reviewed for 2-Dose Schedules

- Immunogenicity
- Post hoc analyses of efficacy trials
- Post-licensure effectiveness
- Health economic models
- Duration of protection

# Immunogenicity of 2-Dose HPV Vaccination Schedules

- **Immunogenicity trials of 2- vs 3-doses have been conducted for all HPV vaccines**
- **Main analyses are 2 doses in ~9–14 year olds vs 3 doses in women age ~16–26 years**
  - Comparison is the age group and schedule for which efficacy was demonstrated
  - Although the basis of protection after vaccination thought to be neutralizing antibody, there is no established minimum antibody threshold for protection
  - All trials found that antibody response after 2 doses (0,6 months or 0,12 months) in ~9–14 year olds is non-inferior to the antibody response after 3 doses in older age group
- **Some trials compared 2 vs 3 doses in ~9–14 year olds**
  - Results vary by trial; antibody titers lower after 2 doses vs 3 dose for some HPV types
- **Based on data from immunogenicity trials, regulatory authorities have approved 2-dose HPV vaccination schedules\***

\*Only 9vHPV data on 2-dose schedules submitted to FDA

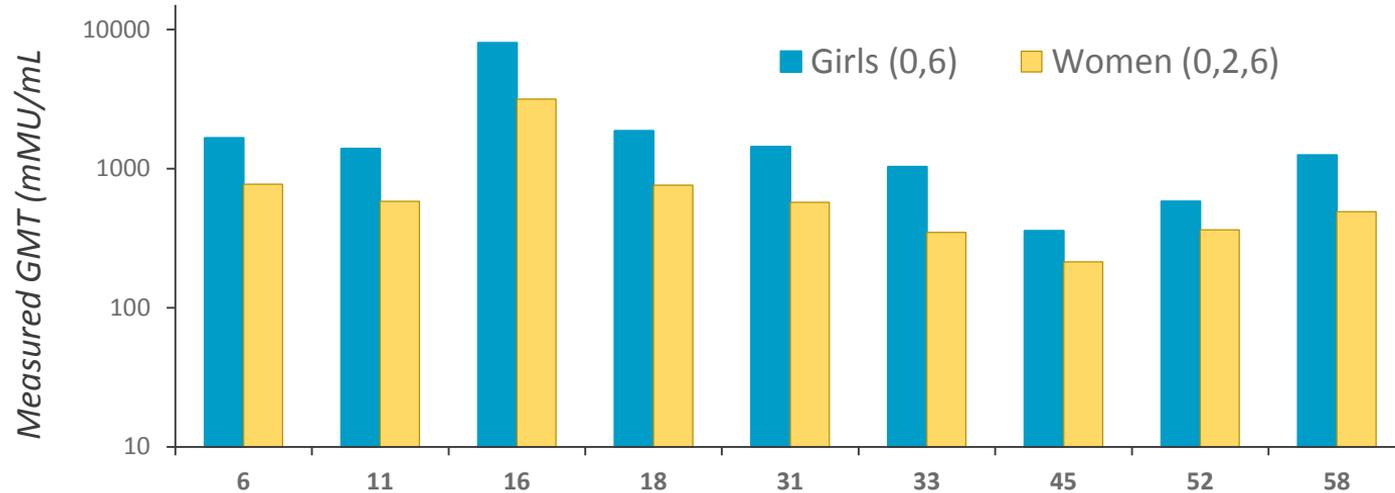
# 9vHPV 2-Dose Trial: Study Design

<b>Enrollment</b>	Open-label study; all received 9vHPV vaccine				
	<b>Cohort</b>	<b>Age (years)</b>	<b>Gender</b>	<b>N</b>	<b>Dosing regimen* (months)</b>
	1	9-14	F	300	0, 6
	2	9-14	M	300	0, 6
	3	9-14	F/M	300	0, 12
	4 (control)	16-26	F	300	0, 2, 6
	5 (exploratory)	9-14	F	300	0, 2, 6
<b>Immunogenicity analyses</b>	<p>Primary analyses at 1 month post-last dose (<i>results presented to ACIP February 2016</i>)</p> <p>Exploratory analyses to assess antibody persistence (<i>Month 12 for cohorts 1, 2, 4, &amp; 5; Months 24 and 36 for all cohorts</i>)</p>				

\*interval window included +/- 4 weeks

# 9vHPV 2-Dose Immunogenicity Trial

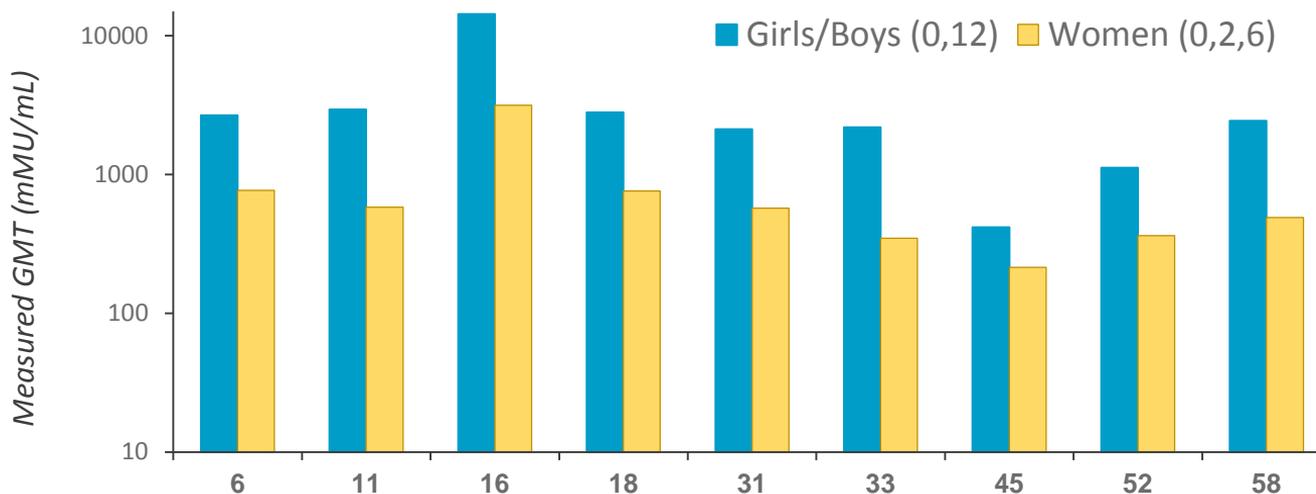
Non-inferior GMT at 1 month post-last dose in  
2-dose girls vs. 3-dose women



<b>Fold difference (girls/women)</b>	<b>2.15</b>	<b>2.39</b>	<b>2.54</b>	<b>2.46</b>	<b>2.51</b>	<b>2.96</b>	<b>1.67</b>	<b>1.60</b>	<b>2.55</b>
<i>95% CI</i>	(1.83, 2.53)	(2.03, 2.82)	(2.14, 3.00)	(2.05, 2.96)	(2.10, 3.00)	(2.50, 3.50)	(1.38, 2.03)	(1.36, 1.87)	(2.15, 3.01)

# 9vHPV 2-Dose Immunogenicity Trial

Non-inferior GMT at 1 month post-last dose in  
2-dose girls/boys vs. 3-dose women



<b>Fold difference (girls &amp; boys /women)</b>	<b>3.47</b>	<b>5.07</b>	<b>4.54</b>	<b>3.69</b>	<b>3.70</b>	<b>6.31</b>	<b>1.96</b>	<b>3.08</b>	<b>4.98</b>
<i>95% CI</i>	(2.93, 4.11)	(4.32, 5.94)	(3.84, 5.37)	(3.06, 4.45)	(3.08, 4.45)	(5.36, 7.43)	(1.61, 2.37)	(2.64, 3.61)	(4.23, 5.86)

# 9vHPV 2-Dose Immunogenicity Trial Summary

- **97.8% – 100% seropositive to all 9 types, 1 month after last dose**
- **Compared with 3 doses in 16–26 year olds, antibody titers after**
  - 2 doses in 9–14 year olds (0,6 months or 0,12 months) were non-inferior, and significantly higher, 1 month after last dose
  - 2 doses in 9–14 year olds (0,6 months) remained non-inferior, and higher, 6 months after last dose
- **GMTs by interval between doses in 2-dose (0,6 months) groups support a minimum interval of 5 months for 2-dose schedule**
- **Follow-up will continue through 36 months**

# FDA Approval of 9-valent HPV Vaccine 2-Dose Series

- FDA approved a 2-dose series for persons age 9–14 years, October 7, 2016
  - Label included data from 2-dose trial and updated Dosage and Administration

----- DOSAGE AND ADMINISTRATION -----  
For intramuscular administration only. (2)  
Each dose of GARDASIL 9 is 0.5-mL  
Administer GARDASIL 9 as follows: (2.1)

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 26 years	3-dose	0, 2, 6 months

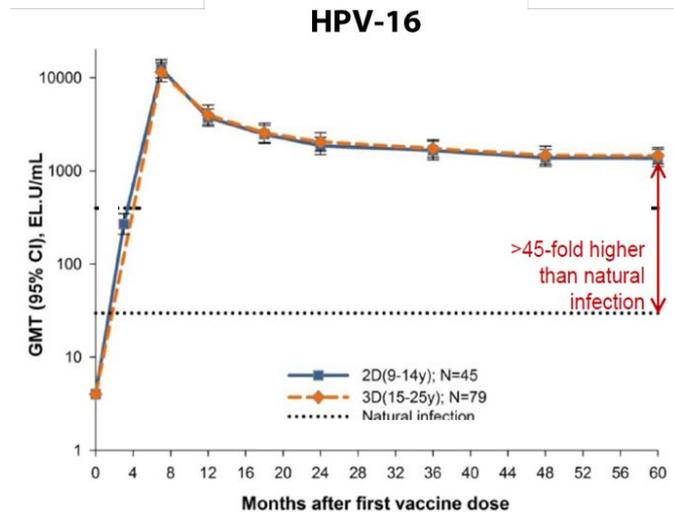
\*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose. (14.2 and 14.5)

# Immunogenicity Data on 2-Dose Schedules for 2vHPV and 4vHPV

- **In all trials, 2 doses (0,6 months or 0,12 months) in ~9–14 year olds were non-inferior to 3 doses in older age group**
  - Longest follow-up in 2- vs 3-dose trials
    - 2vHPV: 60 months
    - 4vHPV: 36 months
    - 9vHPV: 12 months
- **Many individuals have received 4vHPV in the U.S. and some have not completed the 3-dose series**
- **2vHPV and 4vHPV immunogenicity trials were included in GRADE**

# 2vHPV 2- vs 3-Dose Immunogenicity Trial

- **Follow-up through month 60**
  - 2 doses (0,6 months) in 9–14 yr olds
  - 3 doses (0,1,6 months) in 15–25 yr olds
- **Antibody kinetics similar in 2 groups**

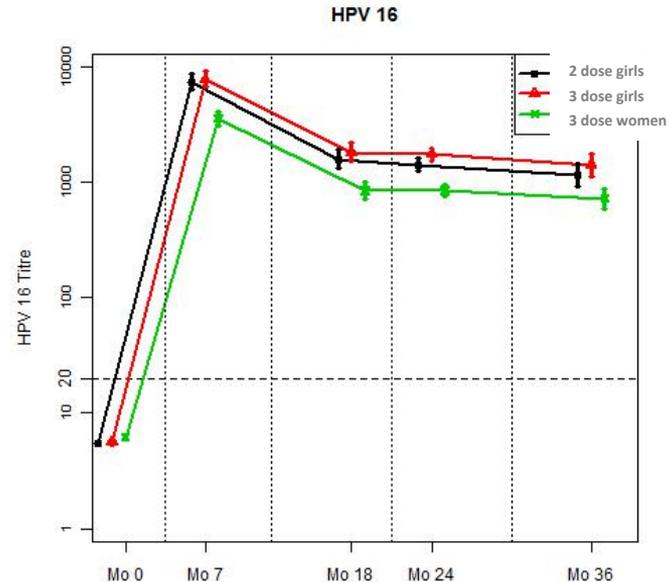


# 4vHPV 2- vs 3-Dose Immunogenicity Trial

## ■ Follow-up through month 36

- 2 doses (0,6 months) in 9–13 yr olds
- 3 doses 0,2,6 months in 9–13 yr olds
- 3 doses (0,1,6 months) in 16–26 yr olds

## ■ Antibody kinetics similar in 3 groups



# Efficacy Data for 2-Dose Schedules

- **No data from randomized controlled trials of 2 doses vs 3 doses of HPV vaccines evaluating efficacy against infection or disease endpoints**
- **2vHPV: data from post hoc analyses of 3-dose efficacy trials**
- **4vHPV: data from analysis of interrupted 2- vs 3-dose efficacy trial that that was analyzed as an observational study**
- **Data from these analyses suggest efficacy with less than a 3-dose schedule**

# Post-Licensure HPV Vaccine Effectiveness Evaluations

- **10 studies evaluated effectiveness by number of doses in settings of a recommended 3-dose schedule for 2vHPV or 4vHPV**
- **Most found 2 doses were not as effective as 3 doses**
- **Limitations of post-licensure effectiveness studies**
  - Most 2-dose vaccinees received vaccine at a 0,1 or 0,2 month interval
  - Persons who only received 2 doses differed from those completing series
    - Older, lower SES, earlier cervical screening
    - Implications for HPV exposure prior to vaccination
- **One study evaluated different intervals between 2 doses**
  - Effectiveness increased as interval between doses increased

# Challenges for HPV Vaccine Effectiveness Evaluation

- **Many methodological challenges using post-licensure effectiveness studies within context of 3-dose program to evaluate 2-dose effectiveness**
- **Data from post-licensure effectiveness studies conducted to date may not be applicable to current policy question due to differences in:**
  - Age at vaccination
  - Interval between 2 doses
  - Differences in populations receiving 2 and 3 doses
- **Post-licensure vaccine effectiveness studies were not included in our evidence for GRADE**

# Modeling and Cost-Effectiveness of 2-Dose Vaccination

## Model

- Individual-based transmission-dynamic model, takes into account herd immunity effects
- Includes 6 components: demographics, sexual behavior and HPV transmission, natural history, vaccination, screening and treatment of cervical lesions and cervical cancer, economics

## Objective

- To evaluate the population-level effectiveness and cost-effectiveness of 3-versus 2-dose 9vHPV vaccination in the U.S.

# Modeling Summary

- If efficacy and duration of protection after 2 doses and 3 doses are similar, 2 doses will be cost-saving compared with 3 doses
- The incremental health benefits and cost-effectiveness of a 3<sup>rd</sup> dose of HPV vaccine depend most on relative duration of efficacy provided by 2 vs. 3 doses
- Vaccination is predicted to reduce HPV-burden of disease substantially if protection >20 years
- 2-dose vaccination will provide similar population-level health benefits to 3-dose vaccination:
  - Unless 2 doses provide shorter duration of vaccine protection AND 2-dose schedules do not enable higher vaccination coverage
- 3-dose vaccination predicted to have high incremental cost per QALY gained (>\$118,000) compared to 2 doses, except when 2-dose protection is <20 years

# Duration of Protection after HPV Vaccination

## No evidence of waning protection after a 3-dose schedule

- Data available through ~ 10 years for 2vHPV and 4vHPV
- Longer follow-up, through 14 years, ongoing in some studies

## Antibody responses maintained over time after a 3-dose schedule

- Data available through ~10 years for 2vHPV and 4vHPV
- Longer follow-up, through 14 years, ongoing in some studies
- Waning of detectable antibody to HPV 18 by cLIA in 4vHPV vaccinees not associated with loss of protection

## 2-dose schedules

- Long term protection data not available from 2-dose trials
- Antibody kinetics similar with 2vHPV and 4vHPV 2-dose schedules (interval between doses ~6 months) in adolescents compared with 3 doses in women

# **GRADE**

**Grading of Recommendations Assessment,  
Development and Evaluation**

# PICO Question

- Should 2 doses of any HPV vaccine be recommended for 9–14 year-olds?
- Population: Girls and boys aged 9–14 years
- Intervention: 2 doses of HPV vaccine, separated by 6–12 months
- Comparison: 3 doses of HPV vaccine, at 0, 1–2, and 6 months, among women in the age group in which efficacy has been demonstrated\*
- Outcome: Immunogenicity

\* Immunobridging studies; analyses with comparison groups age 9–14 years were considered supplemental

# GRADE Summary

Comparison	Outcome	Study design (number of studies)	Findings	Evidence type	Overall evidence type
<b>2 doses (age 9–14) versus 3 doses (age 15–26)</b>	Immunogenicity to 9vHPV types	Observational (1)	Non-inferior immunogenicity	3	<b>3</b>
	Immunogenicity to 4vHPV types	Observational (2)	Non-inferior immunogenicity	3	
	Immunogenicity to 2vHPV types	Observational (4)	Non-inferior immunogenicity	3	

# Considerations for Formulating Recommendations:

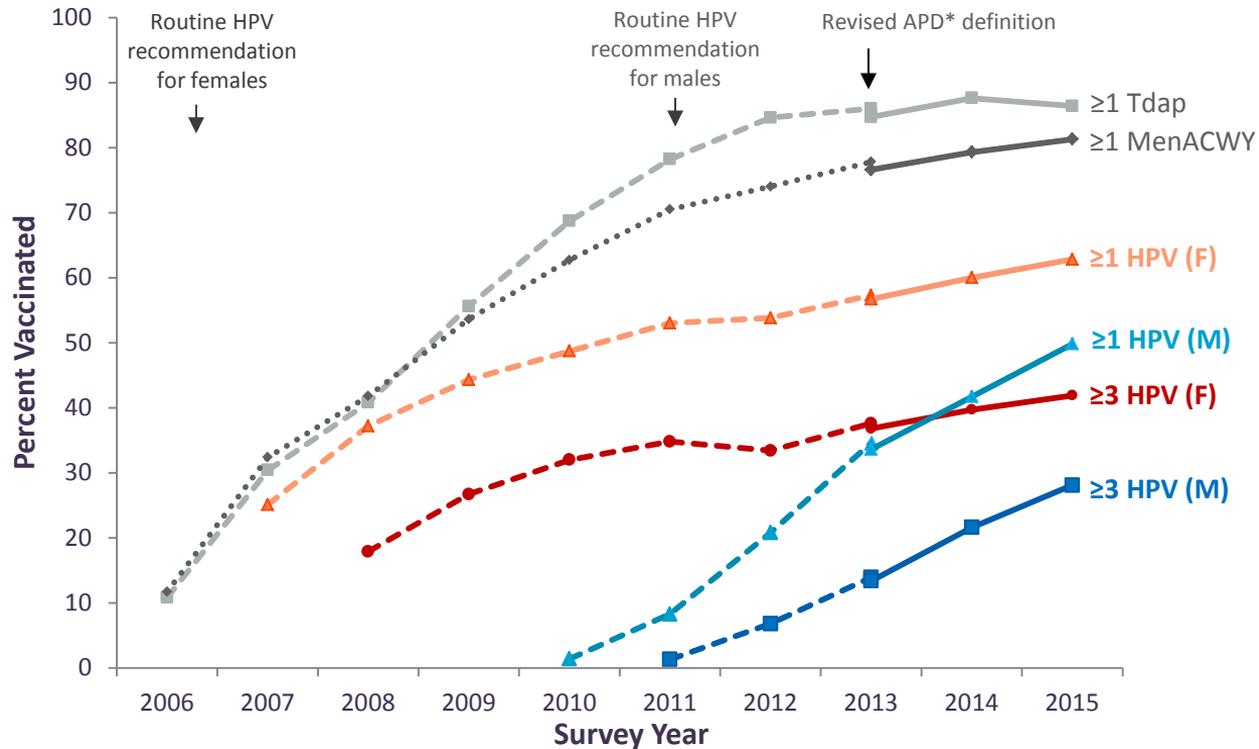
## 2 Doses of HPV Vaccine for Persons Starting the Schedule at Age 9–14 Years

Key Factors	Comments
Balances between benefits and harms	If benefits are expected to be the same and the potential adverse events are lower, then the balance of benefits over harms is greater
Evidence type for benefits	Evidence type 3
Values	High value on programmatic considerations as well as prevention of outcomes due to HPV vaccine types
Cost-effectiveness	Likely cost-effective compared to 3 doses
Summary	Category A recommendation*

\*Proposed; Category A recommendations are made for all persons in an age- or risk-factor-based group

# Programmatic Considerations

# Estimated Vaccination Coverage among Adolescents Aged 13–17 Years, NIS-Teen, United States, 2006-2015



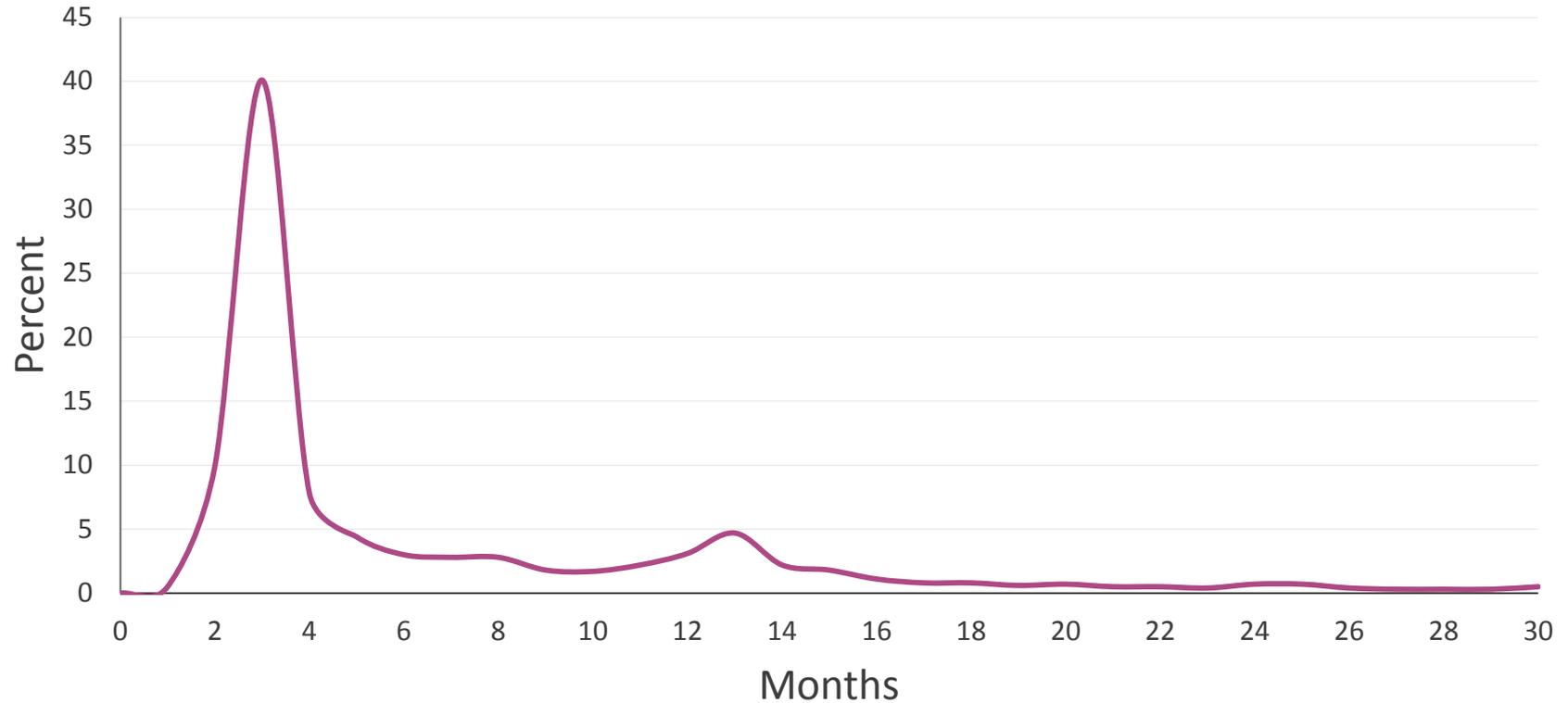
# Programmatic Considerations

- **Unknown if 2-dose recommendation would impact vaccination initiation or series completion**
- **Generally thought that a 2-dose schedule would be easier to implement and more acceptable**
- **Although other countries have switched to a 2-dose schedule, most have school-based vaccination and many already had high coverage**
- **In United States, a 2-dose (0, 6-12 month) schedule would allow flexibility and vaccinations could coincide with preventive health care visits**

# Girls and Boys Aged 13–17 Years Who Received 1, 2, and $\geq 3$ HPV Vaccine Doses, NIS-Teen 2015

	<b>3 doses</b> % (95% CI)	<b>2 doses only</b> % (95% CI)	<b>1 dose only</b> % (95% CI)
<b>Girls</b>	41.9 (40.1-43.7)	10.2 (9.2-11.4)	10.6 (9.6-11.8)
<b>Boys</b>	28.1 (26.6-29.7)	10.9 (9.9-12.1)	10.8 (9.5-12.1)

## Interval (in Months) Between First and Second Dose of HPV Vaccine Among Teens Who Began HPV Vaccination Series Before Age 15 Years (n = 9,410)



## Teens Who Received 2 Doses Only and Teens Who Received 2 Doses Only $\geq$ 5 Months Apart, First Dose Before 15<sup>th</sup> Birthday

Age group (years)	2 doses only % (95% CI)	2 doses only $\geq$ 5 months apart and first dose at <15 years % (95% CI)
13-17	10.6 (9.8-11.4)	5.4 (4.8-6.0)

Denominator is all teens

Data from National Immunization Survey-Teen (NIS-Teen), United States, 2015

# Summary (1)

- **Although three HPV vaccines are licensed for use in the United States, after the end of 2016 only 9vHPV will be available in the United States**
- **In October 2016, FDA approved 9vHPV as a 2-dose series for persons age 9 through 14 years**
- **In 2016, ACIP has been reviewing data related to 2-dose schedules, including immunogenicity, post hoc analyses of efficacy trials, post-licensure effectiveness, health economic models, and duration of protection**
- **Trials of all HPV vaccines found antibody response after 2 doses (0,6 months or 0,12 months) in 9–14 year olds is non-inferior to the response after 3 doses in the group in which efficacy demonstrated**

## Summary (2)

- **Post-licensure studies examining HPV vaccine effectiveness by number of doses are difficult to interpret at this time in the vaccination program**
- **Data from follow-up of 3-dose vaccine trials show that duration of protection after HPV vaccination is long lasting; data from follow-up of immunogenicity trials suggest duration of protection will be the same after 2- and 3-dose schedules**
- **ACIP used GRADE to evaluate evidence on 2-dose HPV vaccination schedules**
- **HPV Vaccines Work Group proposes a Category A recommendation for a 2-dose schedule for persons initiating the series at age 9 through 14 years**
- **A 2-dose HPV vaccination schedule might facilitate vaccine initiation and series completion in the United States**

# ACIP HPV Vaccines Work Group

## ACIP Members

Allison Kempe (Chair)  
Cynthia Pellegrini  
Jose Romero

## Ex Officio Members

Carolyn Deal (NIH)  
Bruce Gellin (NVPO)  
Jeff Roberts (FDA)  
Joohee Lee (FDA)  
Sixun Yang (FDA)

## CDC Lead

Lauri Markowitz

## Liaison Representatives

Shelley Deeks (NACCI)  
Linda Eckert (ACOG)  
Sandra Fryhofer (ACP)  
Amy Middleman (SAHM)  
Chris Nyquist (AAP)  
Sean O'Leary (PIDS)  
Margot Savoy (AAFP)  
Patricia Whitley-Williams (NMA)  
Jane Zucker (AIM)

## Consultants

Joseph Bocchini  
Tamera Coyne-Beasley  
John Douglas  
Sam Katz  
Aimee Kreimer (NCI)  
Debbie Saslow (ACS)  
Rodney Willoughby

# CDC Contributors

Jorge Arana  
Harrell Chesson  
Robin Curtis  
Julianne Gee  
Elissa Meites  
Jeanne Santoli  
Mona Saraiya  
Shannon Stokley  
Lakshmi Sukumaran  
Elizabeth Unger

NIS-Teen data contributed by  
David Yankey  
Laurie Elam-Evans  
James Singleton

# Thank you

For more information, contact CDC  
1-800-CDC-INFO (232-4636)  
TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

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